

Journal Club Spotlights: Current Advancements in Non-Small Cell Lung Cancer



Editor's Note: This is a transcript of a discussion on June 8, 2026. It has been edited and condensed for clarity. To obtain credit for participation [CLICK HERE](#).

Jamie Chaft, MD: Welcome. I am Jamie Chaft, MD, from Memorial Sloan Kettering Cancer Center. In this accredited webinar, we are going to discuss the article from the cooperative groups on chemotherapy combined with immune checkpoint inhibitors for operable stage IIIA/B N2+ non-small cell lung cancer, the AFT46 study (CHIO3). It was published in the May 2026 issue of *Lung Cancer*. I am joined by the lead author of this article, Linda Martin, MD, from the University of Virginia Cancer Center. Dr. Martin, welcome. Thank you for joining us. Please provide an overview and really set the stage for what you were thinking when this trial was designed.

Linda Martin, MD: Thank you. I have been interested in stage III lung cancer ever since I was a fellow. For a long time, the first 10 or 15 years of my career, if patients were operable, it was chemo and radiation, which carried significant toxicity and not a lot of efficacy. There was constantly an interest for how we could innovate in this area and potentially have more patients undergo curative resection and when some of the earliest signals came out in the use of checkpoint inhibitors in stage III lung cancer. Actually, Dr. Everett Vokes approached me because he knew I was trying to come up with a concept and suggested the backbone of this idea to myself and Dr. Jyoti Patel. Initially it did include radiation as well as in the adjuvant setting until the Lung ART trial came out and sort of rendered that moot. We thought if we could use more effective systemic therapies upfront in a potentially operable stage III population that we might have much better, not only local disease control by getting more people to surgery that were potentially operable, but also have that better systemic control where we were not going to see those distant failures that we have been plagued by for such a long time in stage III lung cancer.

Jamie Chaft, MD: Sure. And what were the key objectives of your study?

Linda Martin, MD: We chose an objective that is a little bit unique. It was to look at the clearance of mediastinal N2 nodes from pre- vs posttreatment. Partly the reason for choosing that was that we are optimistic that patients were going to have long disease-free or survival intervals, and we wanted to see if we could use this as an early signal to see if the strategy was going to be a successful one.

Jamie Chaft, MD: And what else did you look at?

Linda Martin, MD: We also looked at some of the traditional outcomes like pathologic complete response (pCR) and major pathological response (mPR), which is less traditional but has become traditional in the interim, as well as event-free survival (EFS) and overall survival (OS), and we certainly wanted to look at any specific issues related to surgery as secondary endpoints.

Jamie Chaft, MD: Your study included patients with stage IIIA and IIIB non-small cell lung cancer and N2+, but our staging system has evolved, so can you make that practical for us?

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Linda Martin, MD: At the time that our protocol was developed, which was in 2017, it became [clear] that there was now a stage IIIA, B, and C. We wanted to include N2 patients that initially we said would be T1 to T3. As the study evolved and as more data came around, we realized there were some T4 patients that also could be considered operable if they were T4 based on size only and it was a more peripheral tumor over 7 cm with single station N2 or low burden of N2 that those could potentially be operable. We adjusted the protocol criteria to allow for up to T4N2, not the T4 invasive type of cases, Pancoast-type cases, or that sort of thing. It was a very small number of T4N2 patients that ultimately enrolled.

Jamie Chافت, MD: What were your other key inclusion criteria?

Linda Martin, MD: They had to be N2 disease, so not T3N1, but we really wanted to focus in on that N2 group, because again, that has just been such a historically challenging group of patients. Other standard criteria included: over age 18 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. And then they had to be deemed potentially resectable by a surgeon at the time of enrollment. It was really important to have surgeon involvement early on. They could not have previous anticancer therapy or any of the major contraindications to checkpoint inhibitors. The N2 nodes, we wanted them to be potentially operable, so they needed to not be bulky. There is a lot of controversy about how to define bulky disease, but we chose to describe it as less than 3 cm with discrete borders. We allowed multistation N2 disease because that was an area to potentially push the envelope, but ultimately, we only had 1 or 2 patients with multistation disease that ended up enrolling.

Jamie Chافت, MD: Did you require these nodes to be pathologically proven or did you accept scan involvement?

Linda Martin, MD: Yes, that was a really key thing. We wanted to be sure that the nodes were proven to be involved and not just on PET scan. And this is based on data that is out there saying if you use PET scan only to establish N2+ disease, that the false positive rate is ~40%, and so you could falsely assume that you have cleared the nodes, but they were never involved to begin with. We felt it was important to have proof of the N2 disease upfront. That is also a reason that it is hard to enroll into these trials, because there is a lot of stringency to the timing of studies, the exact extent of mediastinal sampling. All those other things make it just harder to enroll patients into a study like this, and thus our target for enrollment and our phase 2 rather than phase 3 design were based on those known challenges.

Jamie Chافت, MD: Right, but that is certainly a key factor with your primary endpoint. So kudos for including it.

Jamie Chافت, MD: Was there anything relevant in terms of exclusion criteria?

Linda Martin, MD: We developed this trial in 2017, so we made the exclusion criteria known EGFR mutations at the time. We did not even know to mention ALK or some of the other mutations, but at

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that time it was not yet routine to do EGFR testing on every patient, so we did not feel that we could mandate it. If it had been done and tested and known to be positive, then patients were excluded. If there was N3 involvement, then they would be excluded. Again, there are other features that might be different now. We asked sites to collect PD-L1 data, but it also was not mandatory, and nor was it routinely being done as we were developing the study.

Jamie Chافت, MD: Your trial was single arm multicenter phase 2 study. You had 9 sites enrolling across the US. Could you just walk us through the treatment arms?

Linda Martin, MD: The phase 2 design was to have proven the N2 disease and be deemed potentially operable. Then patients were set to receive 4 cycles of neoadjuvant therapy, which was a platinum-doublet backbone with 1500 mg of durvalumab. The platinum backbone was varied depending on squamous vs nonsquamous histology. Again, trying to be up to date with the standard of care. It is pemetrexed for nonsquamous and docetaxel for squamous. Then restaging was requested to be PET scan, but okay to be CT scan with a goal of operating around 4 to 8 weeks after cycle 4, day 1. Then the resection had to be by lobectomy or greater, and we did not exclude pneumonectomy. We just wanted to make sure it was at least a lobectomy, and it was important that we had good lymph node retrieval during the operation in order to assess our primary endpoint after surgery. Initially, postoperative radiation was going to be optional, and it turned out that with the change in publications and practices that actually none of our patients received postoperative radiation and then scheduled to receive durvalumab for a year. The dosing was set to be every 4 weeks for 13 cycles.

Jamie Chافت, MD: Great. Who did you enroll?

Linda Martin, MD: We enrolled again across 9 different sites, and we had a pretty decent gender mix, about 46% female, 54% male, and median age of 66 years. The majority of patients were ECOG 0, but there were a few ECOG 1 and standard distribution in terms of smoking status. About 65% of patients had adenocarcinoma and the remainder were squamous with 1 large cell patient. Most of the patients were evenly split between T1, T2, and T3, with just a handful of T4 patients, but everyone was N2+ because that was a criteria for enrollment.

Jamie Chافت, MD: You enrolled 37 patients. How many made it to the operating room?

Linda Martin, MD: Thirty patients made it to the operating room, which is 81%. We had predicted that was going to be about our surgical rate, just based on older neoadjuvant trials, and not knowing that many other trials would come out in the interim, all with around the same rate of getting to surgery.

Jamie Chافت, MD: Yes, a pretty typical attrition right there. A key finding of this study showed that 30% of patients had a complete pathologic response. Would you describe these findings in a little more detail?

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Linda Martin, MD: This was based on lymph nodes being clear and primary tumor being rendered as a pathologic complete response. This was based on individual site's reviews, there was no central pathology review. We specifically looked at N2 stations, and which ones cleared and which ones did not. The pathologic complete response was 30%. As far as N2 nodes becoming either N0 or N1, and in most cases it was N0, the N2 node clearance was 73%, so it was 22 of the 30 patients who went to surgery, keeping in mind that we could only measure that endpoint if patients went to surgery.

Jamie Chaft, MD: Of those patients, did any of them have mediastinoscopies and dissections as diagnostic, or was it mostly endobronchial ultrasound (EBUS) at the time?

Linda Martin, MD: I do not have the exact split, but I would say it was ~20% or so had some version of a mediastinoscopy. A few patients had a video-assisted thoracoscopic surgery (VATS) procedure to establish lymph node involvement. That was not required, but it was one of the accepted means for histologic staging, and some people had some combination thereof where they might have had an EBUS but had a VATS of a lymph node that might not have been reachable by EBUS. All had invasive staging beforehand. We did not request or require it to be repeated before surgery, but just to remove those nodes at surgery.

Jamie Chaft, MD: It is such a tricky endpoint, because geographically, some places do these baseline staging so differently. Often to the extent of cutting those nodes out, you do not know how to think about it after induction.

Jamie Chaft, MD: What about safety? What did you find? Any red flags?

Linda Martin, MD: Really no red flags. The chemotherapy-related complications, as a surgeon, seem to be much in line with what we have seen in many other perioperative trial's surgical outcomes. There is a separate manuscript that is going to go into more detail about that. So far, it was overall quite favorable and better than one would expect for a stage III NSCLC patient population in that we had no 30-day or 90-day mortalities, which typically is in the 5% plus range. With these locally advanced cases, only 2 patients required pneumonectomy. That is a 7% rate of pneumonectomy, which in the past has been 10% to 30% in stage III disease. Our completeness of resection was quite good as well. The microscopically margin-negative resection (R0) was 93%, and there were no macroscopic residual tumor (R2) resections. Those things were all better than what we have seen historically in stage III disease before chemoimmunotherapy.

Jamie Chaft, MD: Better drugs is such a great thing. What did you conclude from this study?

Linda Martin, MD: We concluded that this strategy is definitely a viable strategy, that N2 clearance was a lot higher. We had expected it to be over 50%, that was our endpoint, and it was 73%. We had actually intended to accrue a larger number of patients, but because we hit that endpoint so robustly early, the data and safety monitoring board (DSMB) asked us to stop because it did not seem reasonable to continue putting patients on a trial or using the resources if the question had

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been so thoroughly answered. The N2 nodal clearance was much higher than expected. Now that we have other data coming out, secondary analyses, it has been in the 55%-70% range in other studies, so at least it seems to be fairly realistic and consistent. This approach could be done safely with good outcomes and good compliance with therapy. We are still wondering about the attrition rates, how we can do better with that. All of us are wondering about that and what happens to the patients who do not go on to surgery. That's an area of active investigation. We did see significant EFS and OS benefits. We only have 16 months of median follow-up for those endpoints, and certainly there will be additional analyses to look at those longer range endpoints, with this manuscript really focusing on that early endpoint of N2 clearance.

Jamie Chaft, MD: Yes, impressive numbers. So how do you implement this in your day-to-day life? The field has evolved quite a bit. What is the takeaway for patient management?

Linda Martin, MD: Using neoadjuvant radiation, I just do not anymore. That has really changed within our tumor board over the last several years. In practice, a lot of us are starting to adopt an approach that is being studied in some other settings, which is to take patients that look clearly operable, that are stage III, as well as patients that might be operable, the T4N2 patients or patients with multistation disease, where it is a little bit less certain that you could get an R0 resection and start with chemotherapy and immunotherapy. We do have a lot of those patients go on successfully to surgery, and we want to try to have as many able to have that as possible. What is being studied is what happens if you guess wrong on that, and they do not go on to surgery, how many continue on with other local therapy, such as radiation? That is again a question that is being looked at in some other settings and will be of great interest going forward. I think that way in tumor board already. We talk about it as a team as let us start down this road and see if we can get them to surgery. This is such a change. I have been in practice over 20 years, and I have seen such nihilism about surgery and stage III disease, and I know many centers who used to never even consider operating on stage III disease. I have really sensed a shift at our national conferences and within our tumor boards that we are trying to get more patients to surgery in stage III. This paper gives more credibility to that approach.

Jamie Chaft, MD: For those of us who always offered surgery for stage III and were heavily criticized for it, there is a little redemption here. There is likely nothing specifically practice- changing for your study because it is a single arm phase 2 and we have many others in there, but let me ask a different question to draw out from your study. Did you image in the middle of the 4 cycles and perhaps pivot if someone did not look likely to make it to surgery?

Linda Martin, MD: The study did not require it, but nearly every patient got a CT scan after cycle 2. That is where some of the drop off of 37 to 30 patients happened was sometimes after 2 cycles, if it looked like there was disease progression or they were still not looking at all possible to have an R0 resection, then that was the time to change gears and try something different.

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Jamie Chaft, MD: Right. You already answered or proposed a very important unanswered question of what happens to those folks who do not get to surgery. What else do you think we are still waiting for?

Linda Martin, MD: The renewed attention on the tumor board as a team, and keeping track of those patients at multiple steps along the way. Not just seeing them and dismissing them, but keeping track of them along the way, so that if they are not responding, that a pivot can be made in a reasonable fashion, and they do not just get relinquished to palliative care or something along those lines. That is one thing. The other question is to find out what happens in those patients who do a few cycles of systemic therapy and then do chemoradiation? What are their ultimate outcomes, and is that a reasonable strategy? Are we harming them compared to going directly to a PACIFIC study-based regimen? I do not see those being compared necessarily head-to-head, although there are some trials being developed to look at something like that, but I do not know that those will be compared head-to-head. Ultimately, a lot of us would love to know the answer to the question of a chemoradiation adjuvant immunotherapy (IO) strategy vs a strategy that involves surgery. I would love to know how that looks in a randomized fashion, but Dr. Jyoti Patel and I proposed that in anticipation of the study being positive. We wanted to be ready with the next step, and it was disapproved, and I do not think it will ever be approved because randomized trials like that are just incredibly hard to accrue to because of so many differences of opinion and lack of equipoise. I do not see that happening.

Jamie Chaft, MD: Agreed. Yes, the next big question is, what do we do with that quarter of patients who do not clear their N2 nodes? The recently activated cooperative group study looking at proton postoperative radiation therapy (PORT), perhaps there is a role, right? These patients who do not clear their N2 nodes, they do pretty poorly.

Linda Martin, MD: That is going to be a really interesting trial. I am very excited about that trial, and even though it is not a purely surgical question, I am trying to champion it among surgeons, so that they know to consider that. Hopefully, it is a smaller subset who will need it based on this trial, maybe 20%-30% that would be considered for that. All of us are a little unsure of what to do with patients with significant residual disease after surgery, knowing their relapse rate is higher. What modality is going to be most useful to help rescue that situation?

Jamie Chaft, MD: Maybe we will be discussing that trial in another few years. Thank you, Dr. Martin, for joining us today, and for discussing your important study, and congratulations on bringing it home.

Linda Martin, MD: Thank you so much for highlighting it today.